The physiological mechanism for sensing nasal airflow: A literature review

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Background: **Nasal obstruction is a common otolaryngologic complaint, yet the mechanism of sensing airflow is not commonly understood. The objective of this work was to review current knowledge on the physiological mechanism for sensing nasal airflow.**

Methods: **Current literature pertaining to nasal sensation to airflow was retrieved using PubMed and Google Scholar searches.**

Results: **The primary physiological mechanism that produces the sensation of ample nasal airflow is activation of trigeminal cool thermoreceptors, specifically transient receptor potential melastatin family member 8 (TRPM8), by nasal mucosal cooling. The dynamic change in temperature is ultimately sensed. Nasal mucosal cooling is a result of conductive heat loss, driven by temperature gradient, and evaporative heat loss, driven by humidity gradient. The perception of ample nasal airflow is dependent on the overall nasal surface area stimulated by mucosal cooling, which is mainly governed by air flow patterns. Cool thermoreceptors in the nasal mucosa are connected to the respiratory centers and consequently can alter respiration patterns. Mechanoreceptors do not seem to play a role in sensing nasal airflow. Computational fluid dynamics (CFD) modeling could be a valuable objective tool in evaluating patients with nasal congestion.**

Conclusion: **Understanding the physiological mechanism of how the nose senses airflow can aid in diagnosing the cause behind patient symptoms, which allows physicians to provide better treatment options for patients.** **©2014 ARSAAOA, LLC.** © 2014 ARS-AAOA, LLC.

Key Words:
nasal airflow sensation; mucosal cooling; TRPM8; nasal congestion; computational fluid dynamics modeling

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Nasal congestion is an ambiguous term with many synonyms in colloquial conversation and academic discourse. Patients verbalize the sensation of reduced nasal airflow using a myriad of terms. Throughout the literature, rarely is a delineation made between terms referring to subjective perceptions of reduced nasal airflow and those referring to objective measurements. Synonyms for congestion include fullness, obstruction, heaviness, discomfort, blockage, stuffiness, reduced patency, and airflow restriction, among other terminology. For the purposes of this work, nasal congestion will refer to the subjective perception of reduced nasal airflow experienced by patients.

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Nasal airway congestion is a routinely encountered complaint in clinics across the United States. Not only does it negatively impact the quality of life for tens of millions of Americans, it costs the overall healthcare system approximately $6 billion in expenditures.[1] Nasal congestion is often treated pharmacologically. If such treatment fails, as in many cases of anatomic abnormalities, the decision to proceed to surgery is generally based on the surgeon's assessment alone without use of objective testing and these surgeries have reported failure rates ranging from 23% to 37%.[2] Even when objective testing is performed, the results often are not predictive of a patient's professed symptomatic improvement, as numerous studies have found a lack of correlation between subjective and objective measures of nasal airflow.[2–6]

The primary objective tests used to assess nasal airflow are anterior rhinomanometry, acoustic rhinometry, and peak nasal inspiratory flow. Rhinomanometry measures airflow resistance whereas acoustic rhinometry quantifies nasal wall geometry, specifically nasal cavity volume and cross-sectional area. These tests may not correlate well with subjective patient ratings of nasal congestion because the

variables they measure are not primarily involved in the physiological mechanism that senses nasal airflow. For example, nasal resistance to airflow, which is measured by rhinomanometry, decreases by approximately 70% during exercise; however, the majority of people report no improvement of nasal airflow during exercise.[7] Without validated objective clinical tools that correlate well with patient reported nasal congestion, the current diagnosis and treatment of nasal congestion symptoms is based mostly on subjective opinion and patient feedback, which often results in inconsistent outcomes.[4] The burden of nasal congestion on the economy and patients' quality of life, in addition to the lack of correlation between objective and subjective assessments of nasal airflow, warrants a literature review on the physiological mechanism for sensing nasal airflow. A better understanding of what triggers the sensation of nasal congestion can aid in the development of advanced diagnostic tools that correlate with a patient's subjective perception of congestion as well as better treatment outcomes.

Objective assessment of nasal airflow

Current methods of objectively assessing nasal airflow focus on discerning the degree of nasal obstruction attributable to anatomical factors. However, numerous studies have validated the sensation of congestion without any demonstrated anatomical obstruction. Specifically, pharmacologic modulation of trigeminal afferents has been shown to alter perception of nasal airflow. Topical application of local anesthetics in the nostril produces an artificial sensation of nasal congestion with no change in objectively measured airflow, whereas topical application of menthol produces the sensation of decongestion without actually altering nasal morphology.[8] These studies suggest that the perception of nasal airflow has an underlying neurosensory mechanism. The target receptor for menthol has been identified as the nonselective voltage-dependent cation channel transient receptor potential melastatin family member 8 (TRPM8); when combined with cool air, menthol greatly enhances TRPM8 activation and perceived coolness.[9] Stemming from this, researchers investigated the association of temperature and subjective sensation of nasal congestion. The vast majority of these studies came to the conclusion that the primary physiological mechanism that produces the sensation of ample nasal airflow is activation of trigeminal "cool" thermoreceptors by nasal mucosal cooling.[2,4,9–12]

Nasal mucosal cooling mechanism for sensing airflow

A recent study conducted by Zhao et al.[4] examined the effects of air temperature, humidity, nasal mucosal cooling, nasal resistance, and nasal cross-sectional area on perceived nasal congestion by having subjects rate their degree of congestion while sampling air sequentially from 3 facial exposure boxes ventilated with untreated room air, cold air, and dry air, respectively. The room air box and the dry air box were at approximately the same temperature, whereas the cold air box and dry air box had approximately the same absolute humidity. No significant correlation was found between perceived nasal congestion and nasal resistance measured by rhinomanometry, nor between perceived nasal congestion and minimum airway cross-sectional area measured by acoustic rhinometry. Subjects perceived significantly less nasal congestion, both unilaterally and bilaterally, in the cold air box. Subjects also felt less nasal congestion unilaterally when breathing from the dry air box compared with the room air box. This shows that both temperature and humidity are involved in the mechanism of sensing nasal airflow. Additionally, total nasal mucosal heat loss during breathing was calculated by adding conductive heat loss (driven by temperature gradient) and evaporative heat loss (driven by humidity gradient) in order to test whether nasal airflow sensation is mediated by nasal mucosal cooling/heat loss rather than by air temperature or humidity alone. Total nasal heat loss correlated significantly with changes in unilateral and bilateral congestion ratings, which indicates that nasal mucosal cooling is the actual underlying stimulus that activates the trigeminal nerve afferents and results in the perception of a noncongested nose receiving proper airflow.

Along the same lines as Zhao et al.,[4] Sullivan et al.[2] examined the association between perceived nasal congestion and mucosal cooling by constructing 3D computational fluid dynamics (CFD) models that could simulate airflow and heat transfer during inspiration. These variables were compared before and after surgery performed to relieve nasal congestion caused by anatomical abnormalities. The results showed that the average heat flux over the entire surface area of the nasal cavity (nostrils to choana) and over the vestibule of the preoperative nasal mucosa compared to the postoperative nasal mucosa was significantly increased on the originally obstructed side. The surface area where heat flux exceeded a stimulation threshold also showed a statistically significant increase postoperatively in both the entire nasal cavity and in the vestibule on the most obstructed side. Average heat fluxes were higher in the nasal vestibule. Zhao et al.[9] likewise found that the gradient of heat loss throughout the nasal cavity was not uniform but concentrated in the nasal valve and vestibule region. These observations may reflect adaptive optimization to localize high trigeminal sensitivity to areas of greater heat loss, and indeed, the nasal vestibule has been found to contain densely distributed thermoreceptors.[13] Because the nasal vestibule represents the start of the respiratory system and is primarily responsible for alterations in nasal airflow, it follows that the highest concentration of receptors exists in this region to detect and modify the changes in inspired air.[2,14]

Sullivan et al.[2] also examined the association between mucosal heat fluxes and patients' sensation of nasal congestion assessed by Nasal Obstruction Symptom Evaluation (NOSE) and Visual Analog Scale (VAS) scores. Postoperative NOSE scores as well as VAS scores improved in

correlation with a larger surface area stimulated by mucosal cooling. Interestingly, a study done by Zhao et al.[9] found a correlation coefficient between VAS and peak heat flux that is very similar to the correlation coefficient of this study between NOSE and peak heat flux, but stronger than the Sullivan study's correlation between VAS and peak heat flux.[9] In Zhao et al.'s[9] study, computed tomography (CT) scans used to construct CFD models were obtained immediately after data collection, which was not the case in the Sullivan et al.[2] study. This highlights the importance of acquiring CT images shortly after collecting VAS scores to minimize the potentially confounding effects of the nasal cycle. The stronger correlation between NOSE scores and the area stimulated by heat fluxes observed in Sullivan et al.'s[9] study suggests that the best predictor of nasal congestion perception may be the surface area stimulated by mucosal cooling, rather than peak heat fluxes. This provides evidence of an intimate link between airflow and mucosal cooling in the mechanism of sensing nasal airflow.

Nasal mucosal cooling and respiratory drive

Numerous studies have investigated the link between airflow and mucosal cooling and their effects on respiratory drive and timing. In animal experiments, menthol as a specific stimulant of cold thermoreceptors causes respiratory depression.[12] In a study done by Willatt and Jones,[10] peak nasal inspiratory flow readings correlated with symptom scores of nasal congestion as well as nasal lining temperature. Research has documented an association of high intranasal flow rates with low mucosal temperatures and low intranasal flow rates with high mucosal temperatures.[14] A study conducted by McBride and Whitelaw[15] examined the effects of airflow on frequency of diaphragm contractions that occur regularly during breath-holding. The degree of diaphragm contraction inhibition increased with increasing nasal flow and cooler air during inspiration. The effect was no longer observed following local anesthesia of the nose and pharynx.[15] Subsequent studies showed that the ventilatory response to carbon dioxide was inhibited by breathing cool air through the nose.[16] These results support that cool thermoreceptors in the nasal mucosa are connected specifically to the respiratory centers. Thus, if such receptors fail to be stimulated via mucosal cooling, the brain perceives a lack of airflow and consequently produces the sensation of congestion and shortness of breath.

Thermoreceptors and nasal sensation to airflow

Trigeminal afferents bearing TRPM8 "menthol" thermoreceptors are activated when high-speed inhaled air moves through the nostril and induces the evaporation of water from the epithelial lining fluid. The remaining fluid has a lower temperature that leads to reduced fluidity of membrane phospholipids. This change in membrane rigidity is sensed by TRPM8 receptors, causing depolarization of neurons that connect to the brainstem respiratory center.[17] The "cool" message is interpreted as patent nostrils and open lower airways, leading to a decrease in the intercostal and accessory muscle work of breathing. As mentioned before, this receptor fails to activate when anesthetized and induces the sensation of congestion. Similarly, patients who have nasal packing from sinus surgery or any other obstruction in their nostrils as well as laryngectomized patients who do not use their nasal airway, experience nasal congestion as a result of inhibited TRPM8 receptor activation. The brain interprets the lack of stimulation as an "uncool" signal, and provokes apnea, increased work of breathing, or potentially a default increase in sensations that are interpreted as nasal congestion.[17] Responses that induce nasal mucosal thickening or excessive mucus may also partially occlude the airway and limit evaporation, a factor vital for proper mucosal cooling, and consequently reduce the sensation of airflow.

Trigeminal afferents are widely distributed in the nasal mucosa and more than 60% of nasal trigeminal afferents express the TRPM8 thermoreceptor.[18] TRPM8 receptor activation along the nasal septum, lower and middle turbinates, and lateral side wall has been confirmed by recording negative mucosa potentials produced in response to menthol inhalation.[19] TRPM8 nerve fibers have been identified throughout the nasal mucosa within the subepithelium, but they are particularly concentrated around nasal blood vessels, and thus may mediate neurovascular reflexes.[18,20] It has been shown that nebulization of 22°C solutions of saline, histamine, N-acetylcysteine (NAC), and lidocaine decreases superficial nasal blood flow and nasal nitric oxide levels in nonallergic chronic rhinosinusitis subjects, with temperature effects being more potent than histamine H1-receptor–mediated itch, NAC antioxidant, or local anesthetic effects.[21] This data suggests that activation of nasal cool TRPM8 thermoreceptors on trigeminal afferents is linked to local blood vessel vasoconstriction.

The most extensively studied thermoreceptors are those found in the skin. Thermoreceptors can be either cool or warm. Cool thermoreceptors, which are the ones postulated to be involved with the sensation of nasal airflow, are characterized by a transient increase in discharge rate on sudden cooling and a transient inhibition on sudden warming.[10] In addition to this dynamic response, all thermoreceptors show a generally regular static discharge frequency at constant temperature. It has long been recognized that cool receptors in skin respond most strongly to dynamic temperature gradients rather than to fixed temperatures. For example, metal objects like an iron bar are perceived as much cooler than a wooden bar, even at the same temperature, because metal has a higher heat capacity and conducts heat out of the skin much more quickly than does wood. Results of a study by Zhao et al.[4] demonstrated that nasal airflow sensation is mediated by nasal mucosal cooling rather than by air temperature or humidity alone,

which substantiates that the cool sensors inside the nose may function in the same way as skin cool thermoreceptors.

Mechanoreceptors and nasal sensation to airflow

Mechanoreceptors in the nasal mucosa have been studied for their potential role in sensing airflow. In a study investigating rabbit nasal airway receptors, air blown directly at the nasal membrane did not activate mechanoreceptors.[22] In a study examining afferent nerve activity within the nose of a cat, modulations of afferent impulses ceased with occlusion of the nares despite the pressure increase in the nasal cavity and no excitation of mechanoreceptors during breathing was observed.[23] In a study comparing patient nasal congestion ratings and different variables modeled by CFD, no correlation was detected between subjective sensation of nasal airflow and nasal wall shear stress.[11] Nasal wall shear stress is hypothesized to be the effect of airflow that would potentially stimulate mechanoreceptors in the nasal mucosa. These results, combined with the studies already discussed, suggest that nasal airflow sensation is due mainly to the activation of cool thermoreceptors in the nasal airway, rather than the stimulation of mechanoreceptors.

Nasonasal reflexes

Neural pathways exist within the nose, termed nasonasal reflexes.[21] These generally refer to systems where stimulation of afferent nerves in 1 nostril results in activation of bilateral nasal efferent nerves. For example, unilateral application of histamine to the nasal mucosa results in contralateral secretion production that is at least 50% of the amount produced on the stimulated side. The afferent limb of the reflex arc can be inhibited by anesthesia of the ipsilateral trigeminal nerves and the efferent limb of the reflex arc can be inhibited by application of topical anticholinergics to the mucosa of the contralateral nare.[21] Abnormalities in the parasympathetic reflex arcs may contribute to the development of congestion. Researchers have suggested that vasomotor, idiopathic, or "irritant" rhinitis, all conditions that have the primary symptom of nasal congestion, may result from increased sensitivity of afferent fibers to irritant stimuli and/or augmented glandular responses to activation by parasympathetic axons.[24] A growing body of evidence has also indicated that neurotransmitter phenotypes of primary afferent neurons are highly plastic and may change rapidly as a function of exposure to inflammatory stimuli, meaning inflammation induces release of specific molecules that initiate particular signal transduction pathways within afferent neurons, consequently changing the properties of primary sensory neurons.[24] Such alterations may contribute to the sensation of congestion in the absence of impaired breathing or blocked nasal passages. The actual degree of nasal congestion may be exaggerated when TRPM8 receptor bearing neurons become dysfunctional.

The nasal cycle

The physiologic phenomenon of the nasal cycle is important to consider when discussing the mechanism for sensing nasal airflow. The nasal cycle is defined as a spontaneous, reciprocal, unilateral, and objectively measured decrease in hydraulic diameter, decrease in airflow and turbulence, and increase in resistance, without change in the total nasal airflow; the nasal cycle can be detected in 70% to 90% of humans.[25] More simply, 1 side of the nose is engorged while the other is decongested. Awareness of the nasal cycle seems to occur with nasal pathology (mucosal or structural). The purpose of the nasal cycle is thought to be an evolutionary adaptation that allows for optimal regeneration, moisturizing, and cleaning of nasal mucosa on the "resting" side of the nasal passage.[25] In a study that compared the degree of nasal congestion to bilateral acoustic rhinometry measurements throughout the nasal cycle, the subjective feeling of congestion did not correlate with the changing nostril volumes or cross-sectional areas during the nasal cycle.[21] This was likely because the sum of the left and right nostril volumes and areas remained relatively constant, suggesting that subjects may monitor the total nasal airflow by integrating inputs from both nostrils. Conscious awareness of nasal congestion may be noted only when the total nasal airflow is suddenly reduced. Relating this to mucosal cooling, the perception of ample nasal airflow is maintained throughout the nasal cycle as long as overall cooling of nasal mucosa, rather than that of an individual nostril, does not suddenly decline.

Airflow pattern alterations

Dynamic cooling/heat loss of nasal mucosa is not just a function of the static air temperature or humidity in the environment; it also depends on the interaction between an individual's nasal airway structures and the inspired air flow as well as an individual's baseline thermosensory sensitivities.[4] Given the same static air temperature or humidity, differences in nasal structure and physical conditions may result in varying degrees of nasal mucosal cooling and thus lead to different experiences of nasal airflow among subjects. For example, people with empty nose syndrome (ENS) have wide nasal passages which cause the bulk of the inspired airstream to have little contact with the mucosal wall due to lack of turbulence.[26] This abnormal airflow pattern produces little mucosal cooling, similar to a constricted airway with an insufficient air stream. Using simulations in 3-dimensional (3D) models to study transport patterns in the human nose and its overall air-conditioning capacity, Naftali et al.[27] found that about 60% to 70% of air-conditioning/overall heating of inspired air is carried out by the turbinates and the nearby septal and lateral walls. The predicted efficacy of

nasal air-conditioning was reduced by 12% when the middle turbinate was missing and by 16% when the inferior turbinate was missing. This decrease in efficiency is likely related to subsequent changes in airflow patterns as well as the loss of thermoreceptors in the removed tissue. The simulations also showed that in the absence of the inferior turbinate, a relatively large volume of the inspired air is directed into a wide passageway where air-conditioning is ineffective.[27] Significantly altering the morphology of the nasal passages alters airflow patterns and turbulence. Turbulence is a factor in the process of nasal mucosal cooling. Within regions of turbulent airflow, temperature changes are more pronounced compared with regions of laminar airflow.[14] Turbulent airflow is also required for inspired particulate material to come into contact with nasal mucosa, become firmly adsorbed onto mucus, and be swallowed.[21] Without turbulent airflow, the nasal mucosa cannot carry out its primary functions of air-conditioning and filtering. Treatment of nasal congestion symptoms may need to focus on restoring the patient's optimal mucosal cooling and healthy thermosensory functions.[4] Of note though, ENS appears to involve both altered airflow and poor nerve recovery after mucosal intervention.

Modeling nasal physiology with computational fluid dynamics models

Regional air contact with nasal mucosa and accompanying heat loss/mucosal cooling is difficult to measure but can be quantitatively simulated through CFD models. These CFD models are constructed based on CT or magnetic resonance imaging (MRI) images and thus are sensitive to submucosal morphological changes, such as mucosal swelling or engorgement. CFD models can illustrate nasal physiology through 3D models of airflow, heat, water vapor, and inhaled material transport in anatomically-accurate reconstructions of the nasal passages.[11] The data analyzed in a study done by Kimbell et al.[11] demonstrates that CFD modeling can evaluate nasal physiology variables that correlate with patient symptoms. The ultimate goal of comparing CFD variables and subjective measures of nasal congestion is to find a means of objectively diagnosing the cause of the perceived reduction in nasal airflow in clinical populations and to be able to predict and evaluate treatment outcomes. CFD modeling could prove to be a valuable objective tool in evaluating patients with nasal congestion in the near future.

Conclusion

Recent research has validated that the primary physiological mechanism that produces the sensation of ample nasal airflow is activation of trigeminal cool thermoreceptors, specifically TRPM8, by nasal mucosal cooling. Nasal mucosal cooling is a result of conductive heat loss, driven by temperature gradient, and evaporative heat loss, driven by humidity gradient. The perception of ample nasal airflow is dependent on the overall nasal surface area stimulated by mucosal cooling, which is mainly governed by air flow patterns. Cool thermoreceptors in the nasal mucosa are connected to the respiratory centers and consequently can alter respiration patterns. CFD modeling could be a valuable objective tool in evaluating patients with nasal congestion since these models illustrate the discussed variables involved in mucosal cooling. Understanding the physiological mechanism of how the nose senses airflow can aid in diagnosing the cause behind patient symptoms, which allows physicians to provide better treatment options for patients.

References

1. Stewart M, Ferguson BJ, Fromer L. Epidemiology and burden of nasal congestion. *Int J Gen Med*. 2010;3:37–45.
2. Sullivan CD, Garcia GJ, Frank-Ito DO, Kimbell JS, Rhee JS. Perception of better nasal patency correlates with increased mucosal cooling after surgery for nasal obstruction. *Otolaryngol Head Neck Surg*. 2014;150:139–147.
3. Yepes-Nuñez JJ, Bartra J, Muñoz-Cano R, et al. Assessment of nasal obstruction: correlation between subjective and objective techniques. *Allergol Immunopathol (Madr)*. 2013;41:397–401.
4. Zhao K, Blacker K, Luo Y, Bryant B, Jiang J. Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance. *PLoS One*. 2011;6:e24618.
5. Yaniv E, Hadar T, Shvero J, Raveh E. Objective and subjective nasal airflow. *Am J Otolaryngol*. 1997;18:29–32.
6. Naito K, Kondo Y, Ohoka E, Komori M, Takeuchi M, Iwata S. New aerodynamic aspects of nasal patency. *Rhinology*. 1995;33:26–29.
7. Eccles R. Menthol: effects on nasal sensation of airflow and the drive to breathe. *Curr Allergy Asthma Rep*. 2003;3:210–214.
8. Eccles R, Morris S, Tolley NS. The effects of nasal anesthesia upon nasal sensation of airflow. *Acta Otolaryngol*. 1988;106:152–155.
9. Zhao K, Jiang J, Blacker K, Lyman B, Dalton P. Regional peak mucosal cooling predicts the perception of nasal patency. *Laryngoscope*. 2014;124:589–595.
10. Willatt DJ, Jones AS. The role of the temperature of the nasal lining in the sensation of nasal patency. *Clin Otolaryngol Allied Sci*. 1996;21:519–523.
11. Kimbell JS, Frank DO, Laud P, Garcia GJ, Rhee JS. Changes in nasal airflow and heat transfer correlate with symptom improvement after surgery for nasal obstruction. *J Biomech*. 2013;46:2634–2643.
12. Lindemann J, Tsakiropoulou E, Scheithauer MO, Konstantinidis I, Wiesmiller KM. Impact of menthol inhalation on nasal mucosal temperature and nasal patency. *Am J Rhinol*. 2008;22:402–405.
13. Jones AS, Wright RG, Durnam LH. The distribution of thermoreceptors within the nasal cavity. *Clin Otolaryngol*. 1989;14:235–239.
14. Lindemann J, Keck T, Scheithauer MO, Leiacker R, Wiesmiller K. Nasal mucosal temperature in relation to nasal airflow as measured by rhinomanometry. *Am J Rhinol*. 2007;21:46–49.
15. McBride B, Whitelaw WA. A physiological stimulus to upper airway receptors in humans. *J Appl Physiol Respir Environ Exerc Physiol*. 1981;51:1189–1197.
16. Burgess KR, Whitelaw WA. Reducing ventilatory response to carbon dioxide by breathing cold air. *Am Rev Respir Dis*. 1984;129:687–690.
17. Baraniuk JN. Subjective nasal fullness and objective congestion. *Proc Am Thorac Soc*. 2011;8:62–69.
18. Buday T, Brozmanova M, Biringerova Z, et al. Modulation of cough response by sensory inputs from the nose: role of trigeminal TRPA1 versus TRPM8 channels. *Cough*. 2012;8:11.
19. Meusel T, Negoias S, Scheibe M, Hummel T. Topographical differences in distribution and responsiveness of trigeminal sensitivity within the human nasal mucosa. *Pain*. 2010;151:516–521.
20. Keh SM, Facer P, Yehia A, Sandhu G, Saleh HA, Anand P. The menthol and cold sensation receptor TRPM8 in normal human nasal mucosa and rhinitis. *Rhinology*. 2011;49:453–457.
21. Baraniuk JN, Kim D. Nasonasal reflexes, the nasal cycle, and sneeze. *Curr Allergy Asthma Rep*. 2007;7:105–111.
22. Hoshino T. In vitro electrophysiologic studies on nasal airway receptors of the rabbit. *Ann Otol Rhinol Laryngol*. 1988;97:294–297.
23. Glebovskiĭ VD, Baev AV. [Stimulation of trigeminal receptors of the nasal mucosa by respiratory airflow]. *Fiziol Zh SSSR Im I M Sechenova*. 1984;70:1534–1541. [Russian]
24. Naclerio RM, Bachert C, Baraniuk JN. Pathophysiology of nasal congestion. *Int J Gen Med*. 2010;3:47–57.
25. Beule AG. Physiology and pathophysiology of respiratory mucosa of the nose and the paranasal sinuses. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 2010;9:Doc07.
26. Scheithauer MO. Surgery of the turbinates and "empty nose" syndrome. *GMS Curr Top Otorhinolaryngol Head Neck Surg*. 2010;9:Doc03.
27. Naftali S, Rosenfeld M, Wolf M, Elad D. The air-conditioning capacity of the human nose. *Ann Biomed Eng*. 2005;33:545–553.